Remarks

Claims 1, 5, 7, 12, 17, 21, 23, 28, 33, 57, 62, 65, 69, 70, 75, 78, 82, 84, 89, 90, 94, 97, 101, 103, 107, 108, 110, 114, and 119-201 were previously and are still pending in this application. No new matter has been added.

Allowable Claims

The Examiner has indicated that claims 57, 62, 65, 69, 70, 75, 78, 82, 84, 89, 90, 94, 97, 101, 103, 107, 108, 110, 114, and 143-187 are allowable. The Examiner is thanked for this indication.

The Examiner has indicated that claims 28, 122, 127, 132-133, and 137-138 are objected to only as being dependent on a rejected base claim, but would be allowable if rewritten in independent form. The Examiner is thanked for this indication.

Rejections Under 35 U.S.C. §103

The Examiner reiterated the same assertions made in the Office Action dated January 13, 2004 and maintained the rejection of claims 1, 5, 7, 12, 17, 21, 23, 33, 119-121, 123-126, 128-131, 134-136, 139-142, and 188-201 under 35 U.S.C. 103(a) as being unpatentable over Yoshida et al, Kataoka et al, and Rentsch et al. The Examiner further asserts that the claimed anticancer compounds "embrace various compounds including the compounds of the cited references and of the references in the Declaration." The Examiner also asserts that "although the prior art does not investigate the toxicity resulting from the administration of the parent drug and its conjugate, it implies that the disclosed dosages would be in the safety range unless applicant can prove otherwise."

Applicants' response to the above-maintained rejections and the submitted Declaration by Dr. Balthasar on July 12, 2004 were considered by the Examiner but were not found to be persuasive.

Applicants respectfully request that the Examiner reconsider the rejection for the following reasons. (1) The cited references, taken together, actually teach away from the claimed invention; (2) There is additional prior art of record (US patent 5,580,899, Mayhew et al.) discussed below that teaches away from the claimed invention; and (3) The Examiner has not made a *prima facie* case of obviousness.

The references cited by the Examiner do not teach or suggest the possibility of administering a fatty acid conjugate at a dose *above* the Maximum Tolerated Dose (MTD). In fact, taken together, the cited prior art teaches away from the claimed invention.

Kataoka et al. is the only cited reference that shows comparative data on the MTD of a fatty acid conjugate versus the parent compound. Kataoka et al show an experiment involving a fatty acid-anti cancer drug conjugate, N4-behenoyl-Ara-C. The conjugate was given at a dose of 100-1000mg/kg, IP. This was then contrasted with the parent compound, Ara-C, which was reported to be given at a dosage of 1600 mg/kg IP. Clearly, the conjugate was given at a *lower* dose than the parent compound. Thus, Kataoka et al does not teach administering a fatty acid conjugate at a dose *above* the MTD of the parent compound. This is the opposite of that required by the claimed invention. Therefore, Kataoka at al teaches away from the claimed invention.

The Examiner refers to the Kataoka teachings that the conjugate releases the Ara-C over time. The Examiner states that Kataoka teaches that "the fatty acid endows Ara-C with hydrophobicity and, thus, enables BH-AC to be released slowly in the body and would circulate in the body for a prolonged period of time. While it is true that Kataoka teaches that the conjugated drug has lower solubility in the body fluid and is released slowly to the body, there is no support in Kataoka for the Examiner's conclusion that "a higher dose can be used and tolerated compared to the parent drug."

The Examiner seems to be advancing a personal view that is contrary to the teachings of the prior art and the declaration evidence. The Examiner offers no support nor a reasoned basis for this counter-intuitive conclusion that a drug with lower solubility in body fluid will be less toxic and would be able to be administered in higher doses because a drug that has prolonged circulation would be expected to be more toxic and not less toxic.

The Examiner's view is contradicted by the Kataoka et al. reference itself. As mentioned above, Kataoka et al. administered the conjugate at a *lower* dose than the parent. Also, as pointed out in the Declaration by Dr. Balthasar's (submitted with the previous response), the Examiner's belief also is contradicted by the scientific literature.

Dr. Balthasar provided examples from the literature that demonstrated that slow release of anti-cancer drugs, where the time-course of drug circulation is prolonged, can actually decrease MTD. One example cited by Dr. Balthasar, was a review of phase I clinical studies with topotecan, Rowinsky and Verweij cited data showing that the MTD of topotecan is highly

dependent on the mode of topotecan administration, ranging from 22.5 mg/m^2/d when released into the body over 30 min, to 1 mg/m^2/d when released into the body over 72 h (Rowinsky EK and Verweij J, Review of phase I clinical studies with topotecan, Seminars in Oncology, 24: S20-3-S20-10, 1997). Thus, *less* drug could be administered when the drug was administered more slowly.

Another more recent example provided by Dr. Balthasar was from Dr. Balthasar's work showing that slowing the time course of drug administration *decreases* MTD. In recent work conducted in Dr. Balthasar's laboratory (Lobo ED and Balthasar JP, Pharmacokinetic-pharmacodynamic modeling of methotrexate-induced toxicity in mice, Journal of Pharmaceutical Sciences, 92: 1654-1664, 2003), toxicity induced by methotrexate following intra-peritoneal administration in mice was investigated. The MTD of methotrexate was highly dependent on the time-course of release of the drug. For example, following administration of methotrexate by rapid ("bolus") injection, the authors found that MTD was 760 mg/kg. Following slow release of the dose from an osmotic pump over 72 hours, they found that MTD was dramatically reduced to 3.8 mg/kg. Again, *less* drug could be administered when the drug was administered more slowly. Based on the aforementioned, it is not possible to conclude from reading Yoshida et al. that fatty acid drug conjugates of Ara-C have or can be administered at a MTD exceeding that of Ara-C.

The remaining cited references do not undermine or contradict this teaching away from the invention. Yoshida et al. investigated the administration of a fatty acid conjugate of Ara-C (BH-AC) which was administered at doses ranging from 500mg/m^2 to 1300mg/m^2 by intravenous (IV) drip in 10 patients diagnosed with non-Hodgkin's lymphoma. The dose levels (500, 700, 900, and 1300 mg/m^2) were administered to groups of three patients on a 5-consecutive day schedule. Yoshida et al. did not investigate toxicity resulting from the administration of the parent compound (Ara-C), nor did Yoshida et al. provide pharmacokinetic data on Ara-C administered IV. As such, this reference does not provide a comparison of the MTD of the conjugate versus Ara-C in this treatment group by this mode of administration. Thus, Yoshida et al does not teach anything about the MTD of a conjugate versus a parent compound. Accordingly, it is not possible to conclude from the teachings of Yoshida et al. that fatty acid drug conjugates of Ara-C have a MTD exceeding that of Ara-C .

Rentsch et al. studied 4-N-octadecyl-Ara-C, an alkylated derivative of Ara-C bearing a saturated C18 alkyl group on the Ara-C 4-amino group (not a fatty acid conjugate). This reference discloses no comparative data on dose levels of 4-N-octadecyl-Ara-C relative to dose levels of Ara-C in mice. Rentsch et al, did not investigate the development of toxicity following the administration of Ara-C and/or following administration of the alkylated derivative of Ara-C. Consequently, the teachings of Rentsch et al. do not allow making conclusions about the MTDs of Ara-C and/or conjugates of Ara-C. Also, Rentsch et al. do not support the Examiner's conclusion that the prior art demonstrates that fatty-acid anticancer conjugates allow "increases of the dosage of the conjugated drug without harming the body."

There is also additional prior art of record (US patent 5,580,899, Mayhew et al.) that teaches away from the claimed invention. Mayhew, teaches that the administration of *less*, not more, of the fatty acid conjugated drug. Mayhew specifically teaches administering the fatty acid conjugated drugs described in Mayhew in amounts that are the *same as* or *less than* the amounts used when administering the unconjugated anticancer compounds. See column 9, lines 50-67 and column 12, lines 52-67. Mayhew makes it clear that the dose of the fatty acid conjugated drug would have been expected to be a reduced dose compared to the dose of the unconjugated drug. Thus, Mayhew teaches away from a main feature of the present invention, that is, the administration of anticancer compounds as conjugates in amounts which exceed the MTD of the unconjugated anticancer compound.

In summary, it is clear that none of the references (cited and/or of record) teach or suggest the main and novel feature of the instant invention. On the contrary, the references teach away from the claimed invention. Moreover, the Examiner offers no reasoned basis for his conclusions based upon which the claims were rejected. It, therefore, is believed that the Examiner has not made out a *prima facie* case for rejecting the claims.

In view of the foregoing, Applicants respectfully request that the Examiner reconsider and withdraw the rejection of the claims under 35 U.S.C. 103.

CONCLUSION

A Notice of Allowance is respectfully requested. The Examiner is requested to call the undersigned at the telephone number listed below if this communication does not place the case in condition for allowance.

A three-month extension of time, from January 20, 2005 to April 20, 2005, is requested for response to the Office Action mailed from the Patent Office on October 20, 2004. A check in the amount of $1,020.00 is enclosed for said extension. If there is any additional fee occasioned by this response, including any additional extension fee, that is not covered by an enclosed check, please charge any deficiency to Deposit Account No. 23/2825.

Respectfully submitted,
Webb, et al., Applicant(s)

By: _____

Roque El-Hayek, Reg. No. 55,151
Wolf, Greenfield & Sacks, P.C.
600 Atlantic Avenue
Boston, Massachusetts 02210-2206
Telephone: (617) 646-8000

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